

Comparative study of intraoperative mitomycin C and β irradiation in pterygium surgery

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Abstract

Aims—To compare the rate of recurrence and complication after surgery for primary pterygium performed by one surgeon using either intraoperative mitomycin C or β irradiation.

Methods—A retrospective study was performed of 164 eyes in 164 patients who had undergone primary pterygium surgery. After the pterygium was excised, the bare sclera was covered by sliding adjacent superior conjunctiva. 103 eyes received intraoperative mitomycin C (0.04%, 150 seconds) and 61 eyes β irradiation (total dose 21.6 Gy). The mean follow up period was 20.2 (SD 17.9) months (range 1–66 months). Recurrence was defined as the postoperative regrowth of fibrovascular tissue crossing the corneoscleral limbus.

Results—The recurrence rate after mitomycin C and β irradiation was 8.74% and 23.0% of eyes, respectively, after mean follow up of 17.9 and 31.2 months, respectively. The Kaplan–Meier survival analysis revealed a significantly better outcome for those who had intraoperative mitomycin C (Mantel–Cox log rank analysis, $p=0.031$). The mean interval to recurrence was not significantly different between the two groups. During the follow up, none of the patients showed side effects or reactions related to mitomycin C or β irradiation.

Conclusions—The intraoperative administration of 0.04% mitomycin C is more effective than β irradiation as an adjunctive treatment for pterygium surgery in the patient population examined in this study.

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Since pterygium frequently recurs after simple surgical removal, numerous surgical procedures and adjunctive measures have been devised to prevent the recurrence, including a sliding conjunctival flap to cover the pterygium excisional site,^{1–3} conjunctival autograft transplantation,^{4–7} topical mitomycin C drops,^{3 6–10} intraoperative application of mitomycin C,^{3 7 11–13} and β irradiation.^{14–21} However, a direct comparison of the efficacy of these techniques is difficult, because various factors such as follow up period and the definition of recurrence vary among the studies.

Both mitomycin C and β irradiation are thought to prevent the recurrence of pterygium by inhibiting the proliferation of fast growing cells such as fibroblasts and vascular endothelial cells after pterygium excision.²² However,

to the best of our knowledge, no study so far has compared the effectiveness of mitomycin C and β irradiation as adjunctive therapies for pterygium surgery. The purpose of this retrospective study was to investigate the rate of recurrence and complication after primary pterygium surgery performed by one surgeon using either intraoperative mitomycin C or β irradiation.

Patients and methods

A total of 204 consecutive primary pterygia were excised in 175 patients from January 1992 to December 1996. In 29 patients who were treated bilaterally, the eye operated on first was selected for the analysis. Eleven eyes were excluded from the analysis because those eyes were never observed by us after the surgery; 164 primary pterygia in 164 patients constituted the subjects of this retrospective study (Table 1). We did not perform pterygium surgery on patients under 40 years old during this period, because our previous analysis²³ had shown that a pterygium frequently recurs in patients under 40 years old and a recurrent pterygium often has a more exuberant fibrovascular growth response than the original pterygium. The mean follow up period was 20.2 (SD 17.9) months (range 1–66 months). Patients received one of two treatments after the pterygium surgery: intraoperative mitomycin C (group 1) or β irradiation (group 2). As this was a retrospective study, no attempt was made to randomise the patients to either treatment. However, there was no bias in the choice of treatment. The surgery was performed from June 1993 to December 1996 in group 1, and from January 1992 to June 1996 in group 2. Each pterygium was graded into five groups depending on the degree of its invasion onto the cornea (Table 2).

All surgeries were performed on an outpatient basis at Eguchi Eye Hospital by one surgeon (KE). The surgery technique was as follows: after topical anaesthesia (4% ligno-

Table 1 Preoperative characteristics of patients

| | Mitomycin C | β Irradiation | p Value |
|------------------|-------------|---------------------|---------|
| No of eyes | 103 | 61 | |
| Age (SD) (years) | 64.3 (9.1) | 64.3 (9.8) | 0.99* |
| Range | 41–90 | 41–90 | |
| Sex: | | | 0.68† |
| Male | 49 | 27 | |
| Female | 54 | 34 | |
| Pterygium grade: | | | 0.45† |
| Grade 1 | 13 | 3 | |
| Grade 2 | 50 | 32 | |
| Grade 3 | 26 | 17 | |
| Grade 4 | 13 | 7 | |
| Grade 5 | 1 | 2 | |

*Unpaired *t* test. † χ^2 test.

Table 2 Grading of pterygium

| Grade | |
|-------|---------------------------------------------------------------------------------|
| 1 | The maximum length of the invasion is less than one third of the corneal radius |
| 2 | The maximum length of the invasion is one third of the corneal radius or more |
| 3 | The invasion reaches the pupillary area |
| 4 | The invasion covers the whole pupillary area |
| 5 | The invasion transverse the cornea |

caïne (lidocaine)) and subconjunctival injection of 0.5 ml of 2% lignocaine with 1:200 000 adrenaline (epinephrine) into the body of the pterygium, the head of the pterygium was removed from the cornea with a Beaver 66 surgical blade, and the body of the pterygium was dissected and excised with scissors. Limbal peritomy was continued from the superior edge of resection for a distance twice the amount of limbal tissue already resected. A relaxing radial incision was made at the end of the peritomy and the bulbar conjunctiva was dissected from the Tenon's capsule. Silk 7-0 sutures were used to place the flap covering the exposed sclera. All patients had an eye patch occlusion for 24 hours. In group 1, several small surgical sponges soaked with 0.4 mg/ml mitomycin C solution were placed on the bare scleral bed with the conjunctival layer draped over the sponge. After 150 seconds, the sponges were removed and the ocular surface was irrigated with 100 ml of a balanced salt solution. In group 2, β rays from strontium-90 were applied onto the sclera intraoperatively and 10 days after the surgery (total dose 21.6 Gy). All eyes received postoperative treatment of 0.1% fluorometholone and 0.3% ofloxacin four times a day for 2 weeks, tapered over 4 weeks. Follow up visits were scheduled for postoperative days 1, 7, 14, and 28, and then every 1–2 months. Recurrence was defined as the postoperative regrowth of fibrovascular tissue crossing the corneoscleral limbus and constituted treatment failure.

Data were analysed by the Kaplan–Meier survival analysis with the Mantel–Cox log rank test. The Cox hazard model method was applied in each group to evaluate several variables as possible contributory factors to the recurrence of pterygium. The tested variables were age, sex, and grade of pterygium. All data reported here are mean (SD) unless otherwise specified.

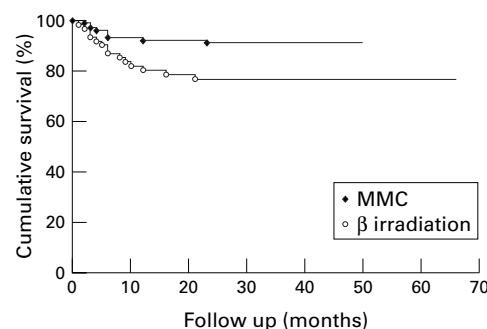


Figure 1 Kaplan–Meier curves showing the cumulative success probability after pterygium surgery with intraoperative application of mitomycin C (0.04%, 150 seconds), or β irradiation (total dosage of 21.6 Gy). There was a statistically significant difference in success probability between the two groups (Mantel–Cox log rank test, $p=0.031$).

Table 3 p Values for each factor's contribution to the recurrence in the two groups

| Explanatory variables | p Value* | |
|-----------------------|-------------|---------------------|
| | Mitomycin C | β Irradiation |
| Age | 0.88 | 0.51 |
| Sex | 0.58 | 0.79 |
| Grade of pterygium | 0.34 | 0.42 |

* p Values calculated by Cox hazard model method.

Results

There was no significant intergroup difference in the distribution of patient sex, age, and pterygium grade (Table 1).

In group 1, the mean follow up period for patients without recurrence was 17.9 months (range 1–50 months). Recurrence occurred in nine eyes (8.74%), and the mean interval to recurrence was 7.2 (6.6) months (range 2–23 months).

In group 2, the mean follow up period for patients without recurrence was 31.2 months (range 1–66 months). Recurrence occurred in 14 eyes (23.0%) at a mean interval of 7.5 (5.7) months (range 1–21 months).

The Kaplan–Meier analysis disclosed a significantly higher survival rate for those who received intraoperative mitomycin C (Fig 1, Mantel–Cox log rank test, $p=0.031$). The mean interval to recurrence was not significantly different between the two groups (unpaired t test, $p=0.76$).

The Cox hazard model method did not reveal any significant contribution of the three explanatory variables (age, sex, and grade of pterygium) to the recurrence in each group (Table 3).

During the follow up, none of the patients showed side effects or reactions related to mitomycin C application or β irradiation. The delay in conjunctival wound healing and the scleral necrosis were not observed in any of the patients.

Discussion

Topical mitomycin C was first used in pterygium surgery by Kunitomo²⁴ and many studies reported the efficacy of postoperative mitomycin C drops in preventing the recurrence of pterygium after surgery.^{3–10} However, various complications of topical mitomycin C have been reported such as corneoscleral melting, cataract, secondary glaucoma, and symblepharon.^{10–25–26} Recently, several studies reported that a single intraoperative application of mitomycin C is an effective and safe treatment in pterygium surgery.^{3–7–11–13} The single intraoperative application of mitomycin C localises the effect on the tissue, abolishes problems of patient poor compliance, and prevents dose dependent complications caused by the inappropriate use of the drug. The minimum effective dosage of intraoperative mitomycin C has been investigated and the application between 0.02% for 3–5 minutes and 0.04% for 3 minutes has been recommended.^{3–13} The dosage we used in the current study (0.04% for 150 seconds) was similar to the recommended range.

The definition of pterygium recurrence after surgery differs among studies and is thought to affect the recurrence rate in each study. In the current study, the recurrence was defined as the postoperative regrowth of fibrovascular tissue crossing the corneoscleral limbus, which was a relatively strict definition. Several studies,^{7 11 12} using a similarly strict definition of pterygium recurrence as ours, reported the recurrence rate of 4–12%. Other studies,^{3 13} utilising milder definition of the recurrence such as the postoperative regrowth of fibrovascular tissue invading more than 1 mm or 1.5 mm into the cornea, reported lower recurrence rate of 4.1–8.6%. The low recurrence rate (8.74%) in the current report, as a study using a strict definition of recurrence, demonstrated the efficacy of sliding conjunctival flap technique combined with intraoperative mitomycin C.

β Irradiation has been used for the treatment of pterygium since the early 1950s and has been shown to reduce the recurrence rate after pterygium surgery to 1.7–12%.^{14–21} The optimal total dosage of β irradiation is thought to be between 10 and 30 Gy given at the time of surgery or within a few days after surgery,^{22 27} to which our regimen corresponds. Among many studies^{14–21} reporting the results of β irradiation for the treatment of pterygium, only a few stated the definition of the recurrence of pterygium. Wilder *et al*²¹ defined the recurrence as regrowth of the pterygium across the bulbar conjunctiva, which was as strict a definition as ours, and reported the recurrence rate of 12.8%. Cooper¹⁸ defined the recurrence as sufficient regrowth to warrant retreatment, which was a less strict definition than ours, and reported the recurrence rate of 11.8%. Compared with those studies, the recurrence rate in group 2 in our study (23.0%) was high. This high recurrence rate may be due to the difference in the surgical procedure employed, total dose of irradiation, follow up times, and dropout rates. However, the purpose of this study was to compare the efficacy of intraoperative mitomycin C and β irradiation as an adjunctive therapy after pterygium surgery, and comparison of the results with other studies was not attempted.

In the current study, the recurrence rate after the same surgical procedure performed by one surgeon was compared between the mitomycin C treated eyes and the β irradiation treated ones. The survival analysis revealed a significantly lower recurrence rate for those who received intraoperative mitomycin C. This result indicates that intraoperative mitomycin C is more effective than β irradiation as an adjunctive treatment for pterygium surgery using a sliding conjunctival flap.

There have been several randomised trials comparing adjunctive therapies after primary pterygium surgery. Chen *et al*⁶ reported that a conjunctival autograft technique and low dose topical application of mitomycin C were equally effective as adjunctive treatments. Manning *et al*⁷ reported that intraoperative mitomycin C offered a lower recurrence rate than conjunctival autograft transplantation

and postoperative mitomycin C drops. The results from the current study together with those reports indicate that intraoperative mitomycin C is an effective treatment with low toxicity among the adjunctive therapies available at the present time.

As a retrospective study, the current study has intrinsic flaws in the methodology. Firstly, no attempt was made to randomise the patients to either treatment. Thus, the study protocol did not guarantee the validity to compare the two treatments. However, as a result, the distribution of pterygium grades, age, and sex were similar in the two groups, which gave us the propriety to compare the two treatments. Secondly, cases with relatively short follow up times were included in the study. Nevertheless, we could properly compare the effectiveness of the two treatments using the Kaplan–Meier survival analysis. The problem is that pterygium recurrence may occur anywhere from 1 to 12 months after the surgery, and cases with less than 6 months could have experienced a recurrence subsequent to their last clinic visit. This means that the current study can not tell the true rate of recurrence of the study treatments.

In 1990, we stopped performing pterygium surgery on patients under 40 years old, because our previous study²³ showed that a pterygium frequently recurs in patients under 40 years old and a recurrent pterygium often has a more exuberant fibrovascular growth response than the original pterygium, as confirmed by other reports.^{6 22} In the current study, we did not find a significant association between patient age and recurrence rate. This result seems to be attributable to the fact that no person under the age 40 was included in this study.

Since the surgery in group 2 was started about 1 year earlier than in group 1, group 2 had longer follow up period. One can argue that the improved prognosis in group 1 may have resulted from them being operated on later when the surgeon had more experience with the surgical technique. However, the surgeon had performed the pterygium surgery using a sliding conjunctival flap technique on over 500 eyes since 1979, and thus the influence of technical learning curve appears negligible in the current series.

While β irradiation reduces the recurrence rate of pterygium, significant long term complications, such as scleral necrosis and secondary infections, have been reported.^{15 28–30} The average latency between β irradiation and the onset of these complications was reported to be over 10 years.³⁰ Vision threatening long term complications such as scleral necrosis and secondary glaucoma have also been reported after topical mitomycin C.^{10 25 26} While intraoperative mitomycin C needs less total dosage and is delivered in a more controlled manner than the topical mitomycin C drops, the application of intraoperative mitomycin C might cause similar long term complications. Thus, we need to perform even longer term follow up of the patients enrolled in the current study.

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